

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-187

CORRESPONDENCE



CONFIDENTIAL

Organon Inc.

September 28, 2001

Susan Allen, M.D., Director
Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation II
Document Control Room 17B45
5600 Fishers Lane
Rockville, Maryland 20857

ORIGINAL



ORIG AMENDMENT

BL

NDA No. 21-187
NuvaRing® (etonogestrel / ethinyl estradiol
vaginal ring)
NDA AMENDMENT
(NuvaRing® Package Insert / Final Draft)

Dear Dr. Allen:

Reference is made to our New Drug Application (No. 21-187) for NuvaRing® (etonogestrel / ethinyl estradiol vaginal ring) which was submitted on December 28, 1999. Further reference is made to our September 28, 2001 FDA teleconference during which the remaining unresolved issues involving the NuvaRing package insert were discussed.

Enclosed herein you will find a copy of our final draft for the NuvaRing® package insert (PI). This version of the PI incorporates the various revisions as discussed and agreed upon between Organon and the FDA representatives at this morning's teleconference. We trust that the enclosed package insert adequately reflects the agreements reached during the teleconference, and request that the Agency contact the undersigned if there are any discrepancies.

This NDA submission is being provided in both electronic and paper format (1 volume). The electronic files are supplied on one (1) CD-ROM [file size is approx. 636 kB]. The CD-ROM has been checked for viruses using McAfee VirusScan (v4.5.0.534). The CD-ROM is being provided under separate cover, directly to the Electronic Document Room.

Please note that Organon Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of 18 U.S.C. and Title 21 of the Code of Federal Regulations.

Should you have any questions or comments concerning this submission, please contact Edward Nellis at (973) 325-4904.

Sincerely,

Edward Nellis (for)

Edwina Muir
Director, Regulatory Affairs

Enclosures
FDA Form 356h

Archival Copy (1 volume)
Medical Review Copy (1 volume)

Submitted via Federal Express Airbill No. 8300 3116 1031

REVIEWS COMPLETED	
DISPOSITION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> MAIL <input type="checkbox"/> MEMO
INITIALS	DATE



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CONFIDENTIAL

September 28, 2001

Susan Allen, M.D., Director
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Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation II
Document Control Room 17B45
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ORIG AMENDMENT

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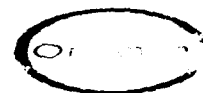
NDA No. 21-187
NuvaRing® (etonogestrel / ethinyl estradiol
vaginal ring)
NDA AMENDMENT
(Change in Room Temperature Storage Period
& Labeling Update to Reflect This Change)

Dear Dr. Allen:

Reference is made to our New Drug Application (No. 21-187) for NuvaRing® (etonogestrel / ethinylestradiol vaginal ring) which was submitted on December 28, 1999. Further reference is made to our September 26, 2001 teleconference during which various NuvaRing® NDA issues were discussed.

Among the topics discussed at the aforementioned teleconference was the issue of the FDA stability requirements for Organon's proposed November 2001 "Scale-Up" sNDA, and the issue involving the storage period for the room temperature storage condition. FDA (Dr. David Lin) had previously recommended that Organon submit 6 months of accelerated data at the time of the sNDA filing (i.e. November 2001), and an additional 3 months accelerated data within two months of filing (for a total of 9 months data). Dr. Lin had stated that these stability requirements were due to concerns with the "burst effect" noted with some registration batches beyond the 6 month time point (at the room temperature condition). Since Organon would not be able to comply with these requirements (for 9 months stability data) and still meet the project timelines, Organon made the following proposal:

On the condition that the requirement for 9 months accelerated stability data is reduced by FDA (to 3 months accelerated data at the time of sNDA submission, with an additional 3 months accelerated data to be provided within 2 months of sNDA submission), Organon agrees to reduce the out of refrigeration (room temperature) storage period from "7 months" (as currently indicated on the product labeling) to "4 months". The change in the room temperature storage period from 7 months to 4 months would be filed as a "CBE" supplement immediately following NDA approval (and prior to submission of the sNDA in November 2001). It was further clarified that "accelerated" stability data would include both the 25°C. storage conditions.



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Susan Allen, M.D., Director
September 28, 2001
Page 2

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During our September 6, 2001 teleconference with Dr. Lin he had indicated that the foregoing Organon proposal would satisfy his concern regarding the burst effect observation, and he agreed to the proposal. During yesterday's teleconference (September 26th) the Agency representatives asked if we could reiterate our discussions with Dr. Lin (since Dr. Lin was temporarily out of the office). After Organon had described the foregoing agreement, Dr. Moo Jhong Rhee requested that the change in the room temperature storage period be filed to the NDA before approval (rather than as a "CBE" post-approval). Organon agreed to this request.

Enclosed herein please find the following documentation in accordance with the agreement reached at our September 26th teleconference:

1. Revised shelf-life / storage condition for drug product.
2. Revised labeling to reflect the change in the shelf-life / storage condition.

This NDA submission is being provided in both electronic and paper format (1 volume). The electronic files are supplied on one (1) CD-ROM [file size is approx. 2.37 MB]. The CD-ROM has been checked for viruses using McAfee VirusScan (v4.5.0.534). The CD-ROM is being provided under separate cover, directly to the Electronic Document Room.

The local FDA Field Office (North Brunswick, NJ) is hereby being notified of this NDA Amendment by copy of this cover letter. A full (identical) copy of the submission will be provided to the local Field Office upon request.

Please note that Organon Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of 18 U.S.C. and Title 21 of the Code of Federal Regulations.

Should you have any questions or comments concerning this submission, please contact Mr. Edward Nellis at (973) 325-4904.

Sincerely,

Edwina Muir (for)

Edwina Muir
Director, Regulatory Affairs

Enclosures
FDA Form 356h

Archival Copy (1 volume)
Chemistry Copy (1 volume)

Submitted via Federal Express Airbill No. 8300 3116 1010

cc: Food and Drug Administration
120 North Center Drive, Bldg C
North Brunswick, NJ 08902
(Cover Letter Only)
Submitted via Federal Express Airbill No. 8300 3116 1009

REVIEWED	
DATE	
CSO INITIALS	
DATE	



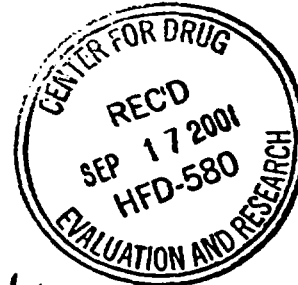
ORIGINAL CONFIDENTIAL

Organon Inc.

September 13, 2001

LF

Susan Allen, M.D., Director
Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation III
Document Control Room 17B45
5600 Fishers Lane
Rockville, Maryland 20857



NDA No. 21-187
NuvaRing® (etonogestrel / ethinyl estradiol vaginal ring)
General Correspondence:
Phase IV Commitment
(Final Protocol for Antimycotic/Tampon
Study No. 34232)

Dear Dr. Allen:

Reference is made to our New Drug Application (NDA No. 21-187) for NuvaRing® (etonogestrel/ ethinyl estradiol vaginal ring), which was originally submitted on December 28, 1999. Reference is also made to our December 20, 2000 NDA correspondence wherein Organon agreed to conduct **Phase IV clinical studies to determine serum etonogestrel and ethinyl estradiol concentrations**, and ovulation inhibition, after multiple doses of a commercially available, oil based anti-mycotic preparation (see page 1 of the December 20th letter/ item-2). In the December 20th correspondence, Organon also agreed to conduct **studies to determine the effects of tampon use on the serum concentration of etonogestrel and ethinyl estradiol** (see page 2 of letter / item-3). These commitments are re-stated in FDA's December 22, 2000 NDA Approvable Letter (and again in the April 27, 2001 Approvable Letter). Further reference is made to our June 21, 2001 submission to the NuvaRing IND [redacted] which included a draft clinical study protocol (No. 34232) entitled:

"An open-label, two-arm, randomized, cross-over, pharmacokinetic interaction trial with NuvaRing® and either vaginally administered anti-mycotics or tampons in healthy female volunteers"

Please note that this protocol combined both phase IV commitments (items 2 & 3, mentioned above) into a single study.

In the FDA "Information Request Letter" of July 10, 2001 the Agency had provided comments on our June 21st draft study protocol (as mentioned above). These FDA comments were addressed in our July 19, 2001 response letter which was submitted to the NDA and to the IND [redacted]. On August 16, 2001 Jennifer Mercier (Regulatory Project Manager for NuvaRing) communicated to Organon that the responses in our July 19th letter would be acceptable to the Agency, and requested that a copy of the final (revised) protocol be submitted prior to the start of the study.



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Susan Allen, M.D., Director
September 13, 2001
Page 2

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This letter provides formal notification that our finalized clinical trial protocol (No. 34232) has been submitted to the NuvaRing IND [REDACTED] as of September 13, 2001.

The principle investigator for this study will be Dr. J. van Leperen, MD (Kendle Clinical Pharmacology Unit, Utrecht, The Netherlands). The IEC/IRB is Stichting Therapeutische Evaluatie Geneesmiddelen, Duivendrecht, The Netherlands. The principles of informed consent will be implemented according to the current revision of the Declaration of Helsinki, the ICH Guideline for Good Clinical Practice, and applicable regulatory requirements. The planned clinical trial period will be from October 2001 to February 2002.

Please note that Organon Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of 18 U.S.C. and Title 21 of the Code of Federal Regulations.

Should you have any questions or comments regarding this submission, please contact Mr. Edward Nellis, Assistant Manager of Regulatory Affairs at (973) 325-4904.

Sincerely,

Edwina L. Muir (for)

Edwina L. Muir
Director, Regulatory Affairs

Form FDA 356h

Submitted via Federal Express No. 8244 4434 4452

9/18/01 -

/S/

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE

NDA ORIG AMENDMENT



CONFIDENTIAL

Organon Inc.

August 2, 2001

ORIGINAL

Susan Allen, M.D., Director
Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation III
Document Control Room 17B45
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Rockville, Maryland 20857



NDA No. 21-187
NuvaRing® (etonogestrel/ethinyl estradiol
vaginal ring)
NDA Re-Submission

Dear Dr. Allen:

Reference is made to our New Drug Application for NuvaRing® (etonogestrel / ethinyl estradiol vaginal ring), which was originally submitted on December 28, 1999. Reference is also made to the April 27, 2001 NDA Approvable Letter for NuvaRing®, and to Organon's April 30, 2001 Response Letter wherein we had indicated our intention to amend the application to provide certain additional documentation as requested in the April 27th Approvable Letter.

Enclosed herein you will find our responses to the FDA information requests as listed in the April 27th Approvable Letter. This documentation addresses the information requests in the following general areas:

1. Drug Product Labeling (Package Insert)
2. Safety Update Report
3. Drug Product Container Labeling

The Drug Product Labeling (Package Insert) as proposed by the Agency in the April 27th Approvable Letter has been reviewed by Organon, and most of the FDA proposed text has now been incorporated into the product labeling (PI). However, some revisions to the FDA proposed labeling was deemed necessary. Please refer to the enclosed document entitled "**Organon Responses to FDA Labeling Proposal**" [electronic filename = history.pdf]. This document provides a complete "listing of labeling changes" (as proposed by Organon), along with explanations and justifications for the Organon revisions (where appropriate). A copy of the FDA proposed text (i.e. "**NuvaRing® Physician and Patient Insert**" from the April 27th Approvable Letter) accompanies the "listing" to facilitate review [electronic filename = refpi.pdf]. Page Numbers, Line Numbers, and Page Headers have been added to the FDA proposed text by Organon (for reference purposes). The Organon edits (as mentioned above) have also been added to the FDA proposed text. This "reference PI" should otherwise be identical to the copy provided by FDA with the April 27th Approvable Letter. The page numbers and line numbers (as referenced in the aforementioned "listing of labeling changes") correspond to those on the "reference PI".



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In addition, we are enclosing copies of the Organon proposed labeling (i.e. package inserts) with the edit tracking indicators (and deleted text) removed:

- **31JUL2001 "Combined Physician and Patient Insert"**
[electronic file = proposed.pdf]
- **18JUN2001 "Patient Labeling"**
[electronic file = patient.pdf]

In order to provide a medium for FDA comments on the Organon proposed labeling changes, we are also including with this submission a copy of the **31JUL2001 "Combined Physician and Patient Insert"** (as above) in word processing format [electronic file = proposed.doc]. However, it should be noted that this "Review Aid" (MS Word file on 3.5" diskette) is being provided with the paper (clinical) review copy only (and is not incorporated into the electronic archival copy on CD-ROM).

At this time Organon is requesting a formal meeting (teleconference) with the responsible Agency representatives to discuss the NuvaRing® drug product labeling. We believe that there are now very few remaining unresolved issues (involving the NuvaRing package insert), and we feel that such a meeting would be useful in bringing this matter to closure. We will follow up with the FDA Regulatory Project Manager during the week of August 13th to arrange for a teleconference at the convenience of the Agency representatives.

In the April 27th Approvable Letter, the Agency had also requested that Organon provide a current **Safety Information Update**. A "Safety Update Report" [electronic filename = update.pdf] is enclosed herein.

There was also a request in the April 27th Approvable Letter to "Include an updated estimate of use for drug marketed in other countries", and to "Provide English translations of current approved Foreign Product Labeling not previously submitted". Although NuvaRing® is not (as yet) being actively marketed in any foreign country, N.V. Organon (Oss, The Netherlands) has received Marketing Authorization for NuvaRing® from the Dutch Medicines Evaluation Board (on February 14, 2001). More recently (June 12, 2001), NuvaRing® was also approved in 14 of the European Union member states. "Foreign Product Labeling" (SmPC and UPL) was previously provided with our February 28, 2001 submission.

"Drug Product Container Labeling" (for the sachet foils, and for the outer [secondary] cartons) is also included with this submission (as requested by the Agency). The enclosed labeling is being submitted in both electronic (pdf) and paper format.

This NDA submission is provided in paper (1 volume) and electronic format. Electronic files are supplied on 1 CD-ROM (total file size is approx. 6.22 MB). The CD-ROM was checked for viruses using McAfee VirusScan™ Version 4.0.2 (Scan Engine: 4.0.02 / Virus Definitions: 4.0.4113), and is being provided under separate cover, directly to the Electronic Document Room.

8/6/01 Review pending - B

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE

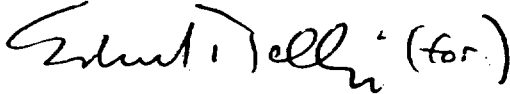
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Should you have any questions or comments regarding this submission, please contact Edward Nellis, Assistant Manager of Regulatory Affairs at (973) 325-4904.

Sincerely,

A handwritten signature in black ink, appearing to read "Edwina L. Muir (for)".

Edwina L. Muir
Director, Regulatory Affairs

Attachment
Form FDA 356h

Archival Copy (1 volume)
Clinical Review Copy: (1 volume)

Submitted via Federal Express No. 8300 3116 1557

0003

ORIG AMENDMENT

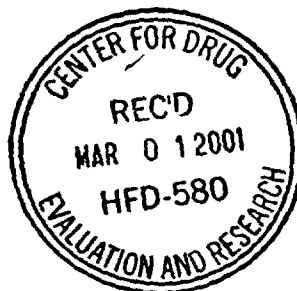


CONFIDENTIAL

Organon Inc.

February 28, 2001

ORIGINAL



Susan Allen, M.D., Director
Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation III
Document Control Room 17B45
5600 Fishers Lane
Rockville, Maryland 20857

B2

NDA No. 21-187
NuvaRing® (etonogestrel/ethinyl estradiol ring)
NDA Re-Submission

Dear Dr. Allen:

Reference is made to our New Drug Application for NuvaRing® (etonogestrel / ethinyl estradiol ring), which was originally submitted on December 28, 1999. Reference is also made to the December 22, 2000 NDA Approvable Letter for NuvaRing®, and to Organon's December 28, 2000 Response Letter wherein we had indicated our intention to amend the application to provide certain additional documentation as requested in the December 22nd Approvable Letter.

Enclosed herein you will find our responses to the FDA information requests as listed in the December 22nd Approvable Letter. This documentation addresses the information requests in the following general areas:

1. Drug Product Labeling (Package Insert)
2. Safety Update Report
3. Foreign Product Labeling

The Drug Product Labeling (Package Insert) as proposed by the Agency in the December 22nd Approvable Letter has been reviewed by Organon, and although the FDA proposed text was generally found to be acceptable, some revisions to this labeling are deemed necessary. Please refer to the enclosed document entitled "**Organon Responses to FDA Labeling Proposals**" [electronic filename = history.pdf]. This document provides a complete "listing of labeling changes" (as proposed by Organon), along with explanations and justifications for the Organon revisions (where appropriate). A copy of the FDA proposed text (i.e. "**NuvaRing® Physician and Patient Insert**" from the December 22nd Approvable Letter) accompanies the "listing" to facilitate review [electronic filename = refpi.pdf]. Page Numbers, Line Numbers, and Page Headers have been added to the FDA proposed text by Organon (for reference purposes). The Organon edits (as mentioned above) have also been added to the FDA proposed text. This "reference PI" should otherwise be identical to the copy provided by FDA with the December 22nd Approvable Letter. The page numbers and line numbers (as referenced in the aforementioned "listing of labeling changes") correspond to those on the "reference PI".



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0001

CONFIDENTIAL

In addition, we are enclosing copies of the Organon proposed labeling (i.e. package inserts) with the edit tracking indicators (and deleted text) removed:

- **27FEB2001 "Combined Physician and Patient Insert"**
[electronic file = proposed.pdf]
- **27FEB2001 "Patient Labeling"**
[electronic file = patient.pdf]

In order to provide a medium for FDA comments on the Organon proposed labeling changes, we are also including with this submission a copy of the **27FEB2001 "Combined Physician and Patient Insert"** (as above) in word processing format [electronic file = proposed.doc]. However, it should be noted that this "Review Aid" (MS Word file on 3.5" diskette) is being provided with the paper (clinical) review copy only (and is not incorporated into the electronic archival copy on CD-ROM).

At this time Organon is requesting a formal meeting (teleconference) with the responsible Agency representatives to discuss the NuvaRing® drug product labeling. We feel that such a meeting would be useful, and may help preclude additional cycles of labeling review and comment. We will follow up with the FDA Regulatory Project Manager during the week of March 5th to arrange for a teleconference at the convenience of the Agency representatives.

In the December 22nd Approvable Letter, the Agency had also requested that Organon provide a current Safety Update Report (in accordance with the information requests outlined on page 2 [items 1-6] of the Approvable Letter). Organon had noted that some of these information requests (e.g. item 2) suggested that the new safety data be fully integrated into the original safety database with a full re-analysis. It is the opinion of Organon that this type of full re-analysis is unwarranted (since the regulations governing safety updates [21 CFR 314.50/d/5/vi/b] do not specifically mention any requirement for re-analysis of the data). It is also stated in FDA's July 1988 "Guideline for the Clinical / Statistical Section of the NDA" (p.45 / "Update of Safety Information") that re-analysis is necessary only when total exposure has been substantially changed (i.e. increased by 25% or more). In the current situation, it has been calculated that the new studies would result in only a 3.3% increase in exposure. Re-analysis would therefore be unnecessary according to the criteria set forth in the FDA guideline.

The foregoing justifications and a proposal for a waiver of the FDA request for integration and re-analysis were submitted to the Agency on January 11, 2001. In a January 24, 2001 follow up teleconference between Ms. Jennifer Mercier (Regulatory Project Manager) and Mr. Edward Nellis (Organon Inc.), Ms. Mercier indicated that the Medical Officer had reviewed our justifications and proposal (as provided in our January 11th submission), and had found them to be acceptable. Based on this discussion, Organon is providing a "**Safety Information Update**" [electronic filename = update.pdf] in accordance with the information requirements outlined in the December 22nd Approvable Letter (except as noted above).

There was also a request in the December 22nd Approvable Letter to "Include an updated estimate of use for drug marketed in other countries" (page 2 / item 6), and to "Provide English translations of current approved Foreign Product Labeling not previously submitted" (on page 3 / item 7). Although NuvaRing® is not (as yet) being actively marketed in any foreign country, N.V. Organon (Oss, The Netherlands) has just received Marketing Authorization for NuvaRing® from the Dutch Medicines Evaluation Board (on February 14, 2001), and is now proceeding with the Mutual Recognition Procedure within the European Union.

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In accordance with the FDA request for "Foreign Product Labeling", we are hereby providing the following labeling materials:

- **"Summary of Product Characteristics" (SmPC) / Dutch Version**
[electronic file = SmPCDut.pdf]
- **"Summary of Product Characteristics" (SmPC) / English Version**
[electronic file = SmPCEng.pdf]
- **"User Package Leaflet" (UPL) / Dutch Version**
[electronic file = UPLDut.pdf]
- **"User Package Leaflet" (UPL) / English Version**
[electronic file = UPLEng.pdf]

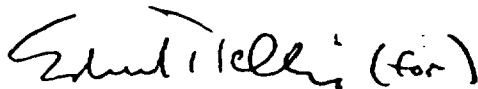
The English versions of the "SmPC" and the "UPL" will be used for the "Mutual Recognition Procedure" to obtain marketing authorizations for the other countries in the European Union.

This NDA submission is provided in paper (1 volume) and electronic format. Electronic files are supplied on 1 CD-ROM (total file size is approx. 2.1MB). The CD-ROM was checked for viruses using McAfee VirusScan™ Version 4.0.2 (Scan Engine: 4.0.02 / Virus Definitions: 4.0.4113), and is being provided under separate cover, directly to the Electronic Document Room.

Please note that Organon Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of 18 U.S.C. and Title 21 of the Code of Federal Regulations.

Should you have any questions or comments regarding this submission, please contact Edward Nellis, Assistant Manager of Regulatory Affairs at (973) 325-4904.

Sincerely,



Edwina L. Muir
Director, Regulatory Affairs

Attachment
Form FDA 356h

Archival Copy (1 volume)
Medical Review Copy: (1 volume)

Submitted via Federal Express No. 8244 4434 0847

REVIEWS COMPLETED	
CSO ACTION	
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CSO INITIALS	DATE

0003

**CONFIDENTIAL**

Organon Inc.

January 11, 2001

Susan Allen, M.D. Director
Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation II
Document Control Room 17B45
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NDA No. 21-187
NuvaRing® (etonogestrel/ethinyl estradiol ring)
General Correspondence:
Proposal for Final Safety Update

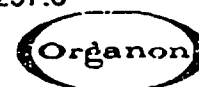
Dear Dr. Allen:

Reference is made to our New Drug Application for NuvaRing® (etonogestrel/ethinyl estradiol ring), originally submitted on December 28, 1999, and to the Approvable Letter dated December 22, 2000.

According to 21 CFR 314.50 (d)(5)(vi)(b) for updates of safety information, which does not make reference specifically to any requirements for reanalysis of data, applicants are encouraged to consult with FDA regarding format and content.

In the July 1988 "Guideline for the Format and Content of the Clinical and Statistical Sections of an Application", pages 45-46 relate to the update of safety information. In this guideline, reference is made to "substantial changes" (i.e., increases in exposure of 25% or more) as being a criteria for an overall analysis of old and new data. For the 120 day safety update submitted in April 2000 and the second safety update submitted in November 2000, Organon presented new information in the same format as the Integrated Summary of Safety Information, however, due to the substantially small increases in exposure, reanalyses of the entire safety database were not performed.

In the original NDA, exposure in the NuvaRing group were as follows:
Adequate and Well Controlled Studies: 068003 and 34219 - 2322 subjects, 23,297.6 cycles of ring use.
Metabolic Studies: 34220, 34221, 34222 - 121 subjects, 634.5 cycles
Local Effects Study: 068004 - 58 subjects, 460.4 cycles



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CONFIDENTIAL

Susan Allen, M.D.
January 11, 2001
Page 2

Currently, the numbers of subjects and cycles for 068004 have increased to a total of 58 subjects (same as original NDA) and 587.9 cycles of exposure. In addition, there are 84 new subjects (67 of these reported in November update) in the ongoing study 34224 (study on endometrium and bone density) with an estimated 700 cycles (470.6 reported previously).

Based on the relatively small numbers of new subjects from the original NDA (84 compared to 2501 - a 3.3% increase) and 827.9 new cycles of exposure compared to the original 24,392.5 (3.3%), Organon proposes that an overall reanalysis of safety data is not necessary for the current safety update, since an impact on the overall safety profile is not expected. To date, NuvaRing has not been marketed in any other countries, therefore, there is no additional exposure from marketing experience.

At this time, we are proposing to submit an Update of Safety Information by presenting only data from the new subjects and/or exposure. We would appreciate FDA's concurrence with this approach.

Please note that Organon Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of 18 U.S.C. and Title 21 of the Code of Federal Regulations.

Should you have any questions or comments regarding this submission, please contact the undersigned at (973) 325-4540, or Ed Nellis at (973) 325-4904.

Sincerely,



Edwina L. Muir
Director, Regulatory Affairs

ELM/hzp

Attachment
Form FDA 356h

Submitted in Duplicate via
Federal Express No 8244 4434 1020

Fax copy to Ms. Jennifer Mercier (HFD-580)

**CONFIDENTIAL**

December 28, 2000

Organon Inc.

Susan Allen, M.D. Director
Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation III
Document Control Room 17B45
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 21-187
NuvaRing® (etonogestrel/ethinyl estradiol ring)
General Correspondence:
Response to Approvable Letter

Dear Dr. Allen:

Reference is made to our New Drug Application for NuvaRing® (etonogestrel/ethinyl estradiol ring), originally submitted on December 28, 1999, and to the Approvable Letter dated December 22, 2000.

Organon is hereby notifying the Agency of our intention to amend the application in the near future.

Please note that Organon Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of 18 U.S.C. and Title 21 of the Code of Federal Regulations.

Should you have any questions or comments regarding this submission, please contact the undersigned at (973) 325-4540.

Sincerely,

Edwina L. Muir,
Director, Regulatory Affairs

ELM/hzp

Attachment
Form FDA 356h

Submitted in Duplicate via
Federal Express No 8198 2930 5527

Fax copy to Ms. Jennifer Mercier (HFD-580)



Organon Inc.
205 Main Street
West Orange
New Jersey, 07062
USA
Tel: (973) 325-4540
Fax: (973) 325-4541

**CONFIDENTIAL**

Organon Inc.

December 20, 2000

Susan Allen, M.D., Director
Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation III
Document Control Room 17B45
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 21-187
NuvaRing® (etonogestrel / ethinyl estradiol ring)
General Correspondence:
(Revised) Phase IV Commitments

Dear Dr. Allen:

Reference is made to our New Drug Application for NuvaRing® (etonogestrel / ethinyl estradiol ring), originally submitted on December 28, 1999, and to our teleconference of December 11, 2000 (during which Phase IV commitments were discussed). Reference is also made to our General NDA Correspondence of December 13, 2000 wherein Organon acknowledged acceptance of the agreed upon Phase IV Commitments. Further reference is made to the December 20, 2000 email from Jennifer Mercier which requested certain additional revisions to the Phase IV Commitments (as described in Organon's December 13th letter).

Enclosed herein you will find the Phase IV Commitments repeated in their entirety (as described in the December 13th Organon letter), with revisions incorporated (as requested by FDA in Jennifer Mercier's December 20th email):

1. Organon will provide FDA with a non-automated alternative for the in vitro release analytical method which would allow FDA to validate the methodology. The alternative will mimic the principles and procedures of the automated method in a manner which can be duplicated by FDA chemists in their own laboratory(ies).

The alternative method will be provided to FDA within one year from the date of FDA's action on NDA 21-187.

2. Organon agrees to conduct a clinical study to determine serum etonogestrel and ethinyl estradiol concentration, and ovulation inhibition, after multiple doses of a commercially available, oil based anti-mycotic preparation. A miconazole nitrate preparation will be used for this purpose (since this was the product which was noted to cause an increase in the AUC value for both EE and ENG following a single dose exposure). A placebo arm with an oil-based vehicle will also be considered. FDA has agreed that for the evaluation of the effects on ovulation inhibition, serum progesterone is considered to be adequate, and that vaginal ultrasonography is therefore not required.

The draft protocol will be submitted within 6 months of the Action date.



Organon Inc.
P.O. Box 1000
Kenilworth, NJ 07033
Tel: 973-325-4769
Fax: 973-325-4770

Susan Allen, M.D.
Page 2
December 20, 2000

CONFIDENTIAL

3. Organon agrees to conduct a clinical study to determine the effects of tampon use on the serum concentration of etonogestrel and EE. FDA has agreed that approximately one week of normal tampon use would be appropriate for the study.

The draft protocol will be submitted within 6 months of the Action date.

4. For postmarketing safety reports of pregnancy following Nuvaring exposure, Organon will attempt to obtain information on the outcome of all such pregnancies including live births, premature births, miscarriages (spontaneous abortions), septic abortions, congenital anomalies and duration of fetal exposure to Nuvaring.

Organon also acknowledges our acceptance of FDA's proposal for a ≤ 30 $\mu\text{g/day}$ limit for the "Day-1 In-Vitro Release for Ethinyl Estradiol".

Please note that Organon Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of 18 U.S.C. and Title 21 of the Code of Federal Regulations.

Should you have any questions or comments regarding this submission, please contact the undersigned at (973) 325-4540, or Mr. Edward Nellis at (973) 325-4904.

Sincerely,



Edwina L. Muir
Director, Regulatory Affairs

Attachment
Form FDA 356h

Archival Copy (1 volume)
Chemistry Review Copy (1 volume)
Clinical Review Copy (1 volume)
Biopharmaceutics Review Copy (1 volume)
Submitted via Federal Express No. 8198 2930 5516



Organon Inc.

CONFIDENTIAL

December 14, 2000

Susan Allen, M.D., Director
Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation III
Document Control Room 17B45
5600 Fishers Lane
Rockville, Maryland 20857

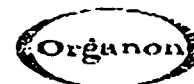
NDA No. 21-187
NuvaRing® (etonogestrel/ethinyl estradiol ring)
Chemistry Amendment

Dear Dr. Allen:

Reference is made to our New Drug Application for NuvaRing® (etonogestrel / ethinyl estradiol ring), originally submitted on December 28, 1999. Reference is also made to the November 8, 2000 teleconference, and to the December 11, 2000 follow up teleconference, during which the NuvaRing® In-Vitro Release Specifications and Acceptance Criteria were discussed with the Agency. Further reference is made to the November 14, 2000 Chemistry Amendment (pages 0016-0017) which prompted the December 11th follow up teleconference.

Enclosed herein please find the **Revised In-Vitro Release Specifications and Criteria** (which are in accordance with the agreements reached with the Agency during the November 8th and December 11th teleconferences). These revised specifications and criteria are also as stated in the FDA Meeting Minutes (for the November 8th teleconference). **Please note that an exact copy of the enclosed documentation has also been provided to the Agency as an electronic email attachment (see December 14, 2000 email to Jennifer Mercier, Regulatory Project Manager for NuvaRing).**

The local FDA Field Office (North Brunswick, NJ) is hereby being notified of this NDA Amendment by copy of this cover letter. A full (identical) copy of the submission will be provided to the local Field Office upon request.



Please note that Organon Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of 18 U.S.C. and Title 21 of the Code of Federal Regulations.

Susan Allen, M.D., Director
December 14, 2000
Page 2

CONFIDENTIAL

Should you have any questions or comments regarding this submission, please contact Mr. Edward Nellis, Assistant Manager of Regulatory Affairs at (973) 325-4904.

Sincerely,



Edwina L. Muir
Director, Regulatory Affairs

EN/cjw

Enclosures
Form FDA 356h

Archival Copy (1 volume)
Chemistry Review Copy: (1 volume)
Biopharmaceutics Review Copy (1 volume)
Submitted via Federal Express Airbill No. 812785700470

cc: Food and Drug Administration
120 North Center Drive, Bldg. C
North Brunswick, NJ 08902
(Cover Letter Only)
Submitted via Federal Express Airbill No. 812785700481

**CONFIDENTIAL**

Organon Inc.

December 13, 2000

Susan Allen, M.D., Director
Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation III
Document Control Room 17B45
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 21-187
NuvaRing[®] (etonogestrel / ethinyl estradiol ring)
General Correspondence: Phase 4 Commitments

Dear Dr. Allen:

Reference is made to our New Drug Application for NuvaRing[®] (etonogestrel / ethinyl estradiol ring), originally submitted on December 28, 1999, and to our teleconference of December 11, 2000 (during which Phase 4 commitments were discussed).

At this time, Organon is acknowledging the following Phase 4 commitments and timelines for completion of same:

1. Organon will provide FDA with a non-automated alternative for the in vitro release analytical method which would allow FDA to validate the methodology. The alternative will mimic the principles and procedures of the automated method in a manner which can be duplicated by FDA chemists in their own laboratory(ies).

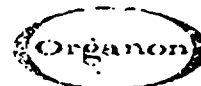
The alternative method will be provided to FDA within one year from the date of FDA's action on NDA 21-187.

2. Organon agrees to conduct a clinical study to determine serum etonogestrel and ethinyl estradiol concentration, and ovulation inhibition, after multiple doses of a commercially available, oil based anti-mycotic preparation. A placebo arm with an oil-based vehicle will also be considered. FDA has agreed that for the evaluation of the effects on ovulation inhibition, serum progesterone is considered to be adequate, and that vaginal ultrasonography is therefore not required.

The draft protocol will be submitted within 6 months of the Action date.

3. Organon agrees to conduct a clinical study to determine the effects of tampon use on the serum concentration of etonogestrel and EE. FDA has agreed that approximately one week of normal tampon use would be appropriate for the study.

The draft protocol will be submitted within 6 months of the Action date.



Susan Allen, M.D.
Page 2
December 13, 2000

CONFIDENTIAL

4. For any pregnancies which are spontaneously reported through postmarketing surveillance, Organon agrees to attempt to obtain follow up data on pregnancy outcome.

Organon also acknowledges our acceptance of FDA's proposal for a ≤ 30 $\mu\text{g/day}$ limit for the "Day-1 In-Vitro Release for Ethinyl Estradiol".

Please note that Organon Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of 18 U.S.C. and Title 21 of the Code of Federal Regulations.

Should you have any questions or comments regarding this submission, please contact the undersigned at (973) 325-4540, or Mr. Edward Nellis at (973) 325-4904.

Sincerely,



Edwina L. Muir
Director, Regulatory Affairs

Attachment
Form FDA 356h

Submitted in Duplicate via Federal Express No. 8235 6570 8530

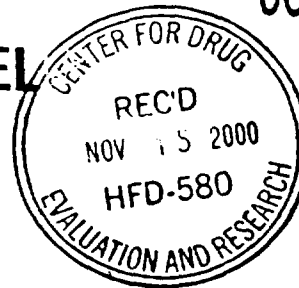
Email copy to Ms. Jennifer Mercier (HFD-580)

AKZO NOBEL

CONFIDENTIAL

Organon Inc.

November 14, 2000



Susan Allen, M.D., Director
Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation III
Document Control Room 17B45
5600 Fishers Lane
Rockville, Maryland 20857

ORIGINAL AMENDMENT

NDA No. 21-187
NuvaRing[®] (etonogestrel/ethinyl estradiol ring)
Chemistry Amendment

Dear Dr. Allen:

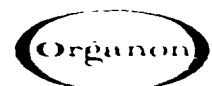
Reference is made to our New Drug Application for NuvaRing[®] (etonogestrel / ethinyl estradiol ring), originally submitted on December 28, 1999. Reference is also made to the September 20, 2000 FDA "Information Request Letter", and to the October 6, 2000 NDA Amendment which provided Organon responses to the FDA information requests. Further reference is made to the **November 8, 2000 FDA/Organon Teleconference** during which outstanding CMC/Biopharmaceutics issues (as related to the NuvaRing NDA review) were discussed.

At this time we are submitting the following documentation which is associated with the November 8th teleconference:

1. **Organon's Meeting Minutes*** (11/08/00 Teleconference)
2. **Organon responses** including additional data and information (as requested by FDA during the teleconference)
3. **Updated Master Batch Record** (and related documentation)

* We trust that the Organon Meeting Minutes (as provided in this submission) accurately reflect the discussions at the November 8th teleconference, and request that the Agency contact the undersigned if there are any discrepancies.

At this time we are also providing formal notification to the Agency that we are withdrawing the Organon West Orange, NJ facility from the NuvaRing NDA (as a "QC Testing Site"). QC testing will be performed at the NV Organon facility (Oss, The Netherlands), with the "In-Vitro Release Test" being performed at [redacted]. Both the NV Organon facility and the [redacted] facility were previously designated as "QC Testing Sites" in the original NDA (Vol:1.6 / p.0240).



For further information regarding the content of this submission, please refer to the brief "Introduction" immediately following the Table of Contents.

CONFIDENTIAL

This NDA submission is provided in paper (1 volume) and electronic format. Electronic files are supplied on 1 CD-ROM (total file size is approximately 1.83 MB). The CD-ROM was checked for viruses using McAfee Vshield Version 4.0.3, and is being provided under separate cover, directly to the Electronic Document Room.

The local FDA Field Office (North Brunswick, NJ) is hereby being notified of this NDA Amendment by copy of this cover letter. A full (identical) copy of the submission will be provided to the local Field Office upon request.

Please note that Organon Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of 18 U.S.C. and Title 21 of the Code of Federal Regulations.

Should you have any questions or comments regarding this submission, please contact Edward Nellis, Assistant Manager of Regulatory Affairs at (973) 325-4904.

Sincerely,



Edwina L. Muir
Director, Regulatory Affairs

Enclosures
Form FDA 356h

Archival Copy (1 volume)
Chemistry Review Copy: (1 volume)
Submitted via Federal Express No. 8198 2930 5479

cc: Food and Drug Administration
120 North Center Drive, Bldg. C
North Brunswick, NJ 08902
(Cover Letter Only)
Submitted via Federal Express No. 8198 2930 5468

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE

Teleconference

0002



CONFIDENTIAL

Organon Inc.

ORIGINAL

November 1, 2000

Susan Allen, M.D., Director
Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation III
Document Control Room 17B45
5600 Fishers Lane
Rockville, Maryland 20857



301

Noted
Gw 11/9/00

NDA No. 21-187

NuvaRing® (etonogestrel/ethinyl estradiol ring)
NDA SAFETY UPDATE

Dear Dr. Allen:

Reference is made to our New Drug Application for NuvaRing® (etonogestrel / ethinyl estradiol ring), originally submitted on December 28, 1999. Reference is also made to our April 27, 2000 NDA Amendment which included the "120 Day Safety Update". Further reference is made to the October 16, 2000 telephone conversation between Ms. Jennifer Mercier (Regulatory Project Manager / NuvaRing®) and Mr. Edward Nellis (Organon Inc) during which Ms. Mercier requested that Organon submit a current "Safety Update" to the NuvaRing® NDA on or before November 10, 2000.

Enclosed herein you will find a current Safety Update Report as requested by the Agency. At the present time, there is only one ongoing study with NuvaRing® (Protocol No. 34224). For the current report, a **cut-off date of October 1, 2000** was applied to the clinical data.

This NDA submission is provided in paper (1 volume) and electronic format. Electronic files are supplied on 1 CD-ROM (total file size is approx. 450 KB). The CD-ROM was checked for viruses using McAfee Vshield Version 4.0.3, and is being provided under separate cover, directly to the Electronic Document Room.

Please note that Organon Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of 18 U.S.C. and Title 21 of the Code of Federal Regulations.



Organon Inc.
375 Mt. Pleasant Avenue
West Orange
New Jersey 07052
USA
Tel.: (973) 325-4500

Susan Allen, M.D., Director
November 1, 2000
Page 2

CONFIDENTIAL

Should you have any questions or comments regarding this submission, please contact Edward Nellis, Assistant Manager of Regulatory Affairs at (973) 325-4904.

Sincerely,

Edwina L. Muir (for)

Edwina L. Muir
Director, Regulatory Affairs

Attachment
Form FDA 356h

Archival Copy (1 volume)
Medical Review Copy: (1 volume)
Statistical Review Copy: (1 volume)
Submitted via Federal Express No. 8235 6570 8493

11/9/00 - NAR Muir, MD

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE

0002



CONFIDENTIAL

Organon Inc.

October 27, 2000

Susan Allen, M.D. Director
Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation III
Document Control Room 17B45
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 21-187
NuvaRing® (etonogestrel/ethinyl estradiol ring)
Clinical Amendment
(Amended Clinical Reports)

Dear Dr. Allen:

Reference is made to our New Drug Application for NuvaRing® (etonogestrel / ethinyl estradiol ring), originally submitted on December 28, 1999. Reference is also made to our July 6, 2000 NDA Amendment which included a summary document describing a re-analysis of the data for clinical study 068003 (and for the ISE). At the request of FDA, a "new revised chart for the 'under 35 age group' based on the re-analysis of the pregnancy data" was also submitted on August 29, 2000. Further reference is made to the September 29, 2000 telephone conversation between Ms. Jennifer Mercier (Regulatory Project Manager / NuvaRing) and Mr. Edward Nellis (Organon Inc.) during which FDA requested that the amended 068003 Study Report (and the amended ISE Report) be submitted to the NDA.

At this time, Organon is submitting in paper and electronic format the amended 068003 Study Report (and the amended Integrated Summary of Efficacy [ISE] Report). The **paper submission (10 volumes) includes:**

- Amended Core Report for 068003 Study (1 volume)
- Amended Appendix-F for 068003 Report (5 volumes)
- Amended ISE Core Report (1 volume)
- Amended Appendix-B for ISE Report (3 volumes)

Copies of the other Appendixes for the 068003 Study Report (i.e. A, B, C, D, E, and I), as well as Appendix-A for the ISE, are not included in the current submission since these appendixes have not been amended and their content remains as in the original submission. Amended Appendixes (G) and (H) for the 068003 Study Report are also being provided in the current submission, but in electronic format only.



Organon Inc.
375 Mt. Pleasant Avenue
West Orange
New Jersey 07057
USA
Tel: (201) 525-4500
Fax: (201) 525-4589

CONFIDENTIAL

The **electronic files** may be found in the following directories (in accordance with the FDA guidance, and as provided in the original electronic NDA submission):

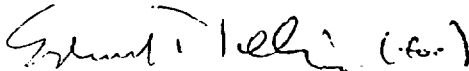
• Amended Core Report for 068003 Study	N21187 \ clinstat \ 068003 \
• Amended Appendix-F for 068003 Report	N21187 \ clinstat \ 068003 \
• Amended Appendix-G for 068003 Report	N21187 \ crt \ Domain \ 068003 \
• Amended Appendix-H for 068003 Report	N21187 \ crt \ Profile \ 068003 \
• Amended ISE Core Report	N21187 \ clinstat \ ise \
• Amended Appendix-B for ISE Report	N21187 \ clinstat \ ise \

The electronic files are supplied on 2 CD-ROMs (total file size is approximately 737 MB). The CD-ROM was checked for viruses using McAfee Vshield Version 4.0.3, and is being provided under separate cover, directly to the Electronic Document Room.

Please note that Organon Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of 18 U.S.C. and Title 21 of the Code of Federal Regulations.

Should you have any questions or comments regarding this submission, please contact Edward Nellis, Assistant Manager of Regulatory Affairs at (973) 325-4904.

Sincerely,



Edwina L. Muir
Director, Regulatory Affairs

EN/cjw

Attachments
Form FDA 356h

Archival Copy (1 volume)
Medical Review Copies (10 volumes)
Statistical Review Copies (10 volumes)

Submitted via Federal Express No. 8235-6570-8449

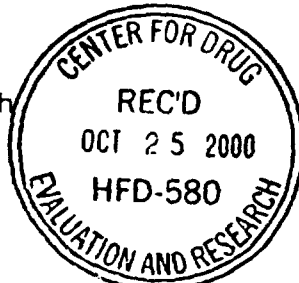


CONFIDENTIAL

Organon Inc.

October 24, 2000

Electronic Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD 20852



ORIGINAL

NDA No. 21-187
NuvaRing® (etonogestrel/ethinyl estradiol ring)
CMC Amendment
(Updated Analytical Method)

CMC AMENDMENT

Dear Sir/Madam:

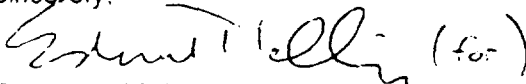
Reference is made to our New Drug Application for NuvaRing® (etonogestrel / ethinyl estradiol ring), originally submitted on December 28, 1999. At this time, we are providing amended CMC documentation in the form of an electronic and paper submission. The submission includes an updated **ethinyl estradiol analytical method for the "Assay and Determination of Related Substances"** (Module #08E / Ver: 01 / ODIN No. NL0020959). Also included with this submission is a copy of the **method validation report** for the aforementioned analytical procedure (Module #14E / Ver: 01 / ODIN No. NL0024292).

The electronic files enclosed herein are supplied on 1 CD-ROM (total file size is approx. 931 kB). The CD-ROM was checked for viruses using McAfee Vshield (ver: 4.0.3). The paper copy has been sent under separate cover to the Division Document Room, HFD-580.

Please note that Organon Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of 18 U.S.C. and Title 21 of the Code of Federal Regulations.

Should you have any questions or comments regarding this submission, please contact Mr. Edward Nellis, Assistant Manager of Regulatory Affairs at (973) 325-4904.

Sincerely,

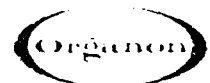
 (for)

Edwina L. Muir
Director, Regulatory Affairs

Attachment
Form FDA 356h

Submitted via Federal Express No. 8235 6570 8438

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE





CONFIDENTIAL

Organon Inc.

October 19, 2000

Ms. Jennifer Mercier
Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation III
Room 17B45
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 21-187
NuvaRing® (etonogestrel/ethinyl estradiol ring)
Foreign Product Labeling

Dear Ms. Mercier:

You had previously requested that Organon submit copies of any (NuvaRing®) foreign product labeling to the NDA. At the present time NuvaRing is not approved for marketing in any foreign country. We are therefore unable to comply with your request at this time since there is no approved foreign labeling currently available for this product.

Please note that Organon Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of 18 U.S.C. and Title 21 of the Code of Federal Regulations.

If you have any questions regarding the above, I can be reached at (973) 325-4904.

Sincerely,

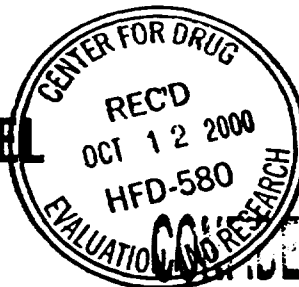
Ed Nellis
Assistant Manager, Regulatory Affairs

EN/nzp

Submitted via Federal Express No. 8198 2930 6637



Organon Inc.
375 Mt. Pleasant Avenue
West Orange
New Jersey 07052
USA
Tel: (973) 325-4500
Fax: (973) 325-4589



Organon Inc.

October 11, 2000

ORIGINAL

Susan Allen, M.D., Director
Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation III
Document Control Room 17B45
5600 Fishers Lane
Rockville, Maryland 20857

MR

NDA No. 21-187
NuvaRing® (etonogestrel / ethinyl estradiol ring).
INFORMATION PACKAGE FOR FDA MEETING

Dear Dr. Allen:

Reference is made to our New Drug Application No. 21-187 for NuvaRing® (etonogestrel / ethinyl estradiol ring) which was submitted on December 28, 1999. Further reference is made to Organon's September 20, 2000 Meeting Request Letter, and to the September 27, 2000 FDA Acknowledgement Letter granting Organon's meeting request.

The aforementioned meeting was requested by Organon to discuss certain **post-approval CMC changes being proposed for the NuvaRing® drug product**. The meeting has been scheduled for **November 16, 2000 at 10 A.M.** in the FDA Parklawn Building (Conference Center, Room "C").

Enclosed herein you will find a pre-meeting documentation package for the November 16th FDA meeting. The package includes background information on the planned post-approval CMC changes, along with descriptions of the proposed studies and documentation intended to support these changes. A copy of the "Meeting Agenda" and a list of "Topics for Discussion" is also included in the package (as provided in the original meeting request letter).

The local FDA Field Office (North Brunswick, NJ) is hereby being notified of this NDA Amendment by copy of this cover letter. A full (identical) copy of the submission will be provided to the local Field Office upon request.



Please note that Organon Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of 18 U.S.C. and Title 21 of the Code of Federal Regulations.

Organon Inc.
375 Mt. Pleasant Ave.
West Orange
New Jersey 07052
USA
Tel.: (973) 325-4500
Fax: (973) 325-4501

San Allen, M.D., Director
October 11, 2000
Page 2

CONFIDENTIAL

Should you have any questions or comments concerning this submission, please contact Mr. Edward Nellis at (973) 325-4904.

Sincerely,



Edwina Muir
Director, Regulatory Affairs

Enclosures
FDA Form 356h
Archival Copy (1 volume)
Chemistry Copy (1 volume)

Submitted via Federal Express Airbill No. 8198-2930-7162

cc: Ms. Jennifer Mercier
Regulatory Project Manager
HFD-580 / 17B45
(Eight [8] DESK COPIES)
Submitted via Federal Express Airbill No. 8198-2930-7130

Food and Drug Administration
North Brunswick, NJ
(Cover Letter Only)
Submitted via Federal Express Airbill No. 8198-2930-7140

REVIEWS COMPLETED

CSO ACTION:

☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS

DATE

0002

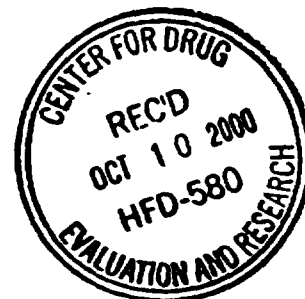


CONFIDENTIAL

Organon Inc.

October 6, 2000

ORIGINAL



Susan Allen, M.D., Director
Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation II
Document Control Room 17B45
5600 Fishers Lane
Rockville, Maryland 20857

ORIG AMENDMENT

A2

NDA No. 21-187
NuvaRing® (etonogestrel/ethinylestradiol ring)
NDA AMENDMENT
(Responses to Reviewer Information Requests)

Dear Dr. Allen:

Reference is made to our New Drug Application (No. 21-187) for NuvaRing® (etonogestrel / ethinylestradiol ring) which was submitted on December 28, 1999. Further reference is made to the September 20, 2000 FDA Letter wherein certain additional information (pertinent to the review of the NuvaRing® NDA) was requested by the Agency.

The Organon responses to the aforementioned FDA information requests are provided herein. A copy of the September 20th FDA "Information Request Letter" is also appended for reference purposes.

This NDA submission is being provided in both electronic and paper format (1 volume). The electronic files are supplied on one (1) CD-ROM [total file size is approx. 825 kb. The CD-ROM has been checked for viruses using McAfee Vshield (version: 4.0.3). The CD-ROM is being provided under separate cover, directly to the Electronic Document Room.

The local FDA Field Office (North Brunswick, NJ) is hereby being notified of this NDA Amendment by copy of this cover letter. A full (identical) copy of the submission will be provided to the local Field Office upon request.



REVIEWS COMPLETED

CSO ACTION:

☐ LETTER ☐ N.A.I. ☐ MEMO

Organon Inc.
375 Mt. Pleasant Ave.
West Orange
New Jersey 07052
USA
Tel (973) 325-4500
Fax (973) 325-4501

Susan Allen, M.D., Director
October 6, 2000
Page 2

CONFIDENTIAL

Please note that Organon Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of 18 U.S.C. and Title 21 of the Code of Federal Regulations.

Should you have any questions or comments concerning this submission, please contact Mr. Edward Nellis at (973) 325-4904.

Sincerely,


Edwina Muir
Director, Regulatory Affairs

EN/cjw

Enclosures
FDA Form 356h

Archival Copy (1 volume)
Pharmacology / Biopharmaceutics Copy (1 volume)
Clinical Copy (1 volume)
Chemistry Copy (1 volume)

Submitted via Federal Express Airbill No. 8235-6570-8596

cc: Ms. Jennifer Mercier
Regulatory Project Manager / NuvaRing®
HFD-580 / 17B45
(THREE [3] DESK COPIES)
Submitted via Federal Express Airbill No. 8235-6570-8574

Food and Drug Administration
North Brunswick, NJ
(Cover Letter Only)
Submitted via Federal Express Airbill No. 8235-6570-8585

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Organon Inc.

CONFIDENTIAL

September 20, 2000

Susan Allen, M.D., Director
Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation III
Document Control Room 17B45
5600 Fishers Lane
Rockville, Maryland 20857



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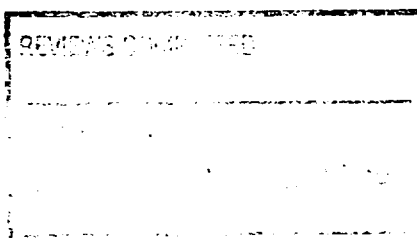
NDA No. 21-187
NuvaRing® (etonogestrel /
ethinyl estradiol ring)
REQUEST FOR FDA MEETING

Dear Dr. Allen:

Reference is made to our New Drug Application No. 21-187 for NuvaRing® (etonogestrel / ethinyl estradiol ring) which was submitted on December 28, 1999. Further reference is made to the July 7, 1999 pre-NDA CMC Meeting during which it was agreed that discussion of certain post-approval CMC changes being proposed by Organon might best be deferred until at least nine (9) months into the NDA review.

At this time we are hereby requesting a meeting with the Division to discuss the aforementioned post-approval CMC changes. A proposed "Agenda" for the meeting is attached. At the meeting the Organon representatives will provide an overview of the proposed CMC changes, and then describe the various studies and documentation intended to support the proposed changes. Our objective for this meeting is to obtain FDA concurrence with regard to the adequacy of our supporting documentation, and to obtain FDA concurrence with our proposed filing mechanism (see "Topics For Discussion", attached).

We would like to propose that this meeting be held at the Agency (Parklawn Building) on either Thursday (**November 16, 2000**), or on Friday (**November 17, 2000**). Due to scheduling difficulties, these two dates are much preferred by the Organon participants. However, if these dates conflict with the schedules of the participating Agency personnel, please contact the undersigned directly to discuss alternative dates for the meeting. For the meeting, we are requesting that the **Chemistry and BioPharm. Reviewers** be in attendance, in addition to other FDA representatives as deemed appropriate by the Agency.



Organon Inc.
375 Mt. Pleasant Av.
West Orange
New Jersey 07052
USA
Tel. (973) 325-450
Fax (973) 325-458

Susan Allen, M.D., Director
September 20, 2000
Page 2

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At the meeting the **Organon participants** will include:

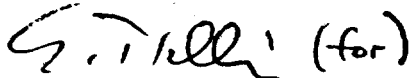
Tom Pituk, PhD, Group Director, (Regulatory Affairs)
Ruud Groenewegen, MSc, Section Head (Product Development)
Marjan van der Werf-Pieters, PhD, Int'l. Project Manager (Reproductive Medicine)
Edwina Muir, Director (Regulatory Affairs)
Ed Nellis, Assistant Manager (Regulatory Affairs)

Organon plans to submit a **pre-meeting documentation package** during the first week of October. We will contact the Agency at that time to determine the number of additional "desk copies" to be provided for the FDA meeting participants.

Please note that Organon Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of 18 U.S.C. and Title 21 of the Code of Federal Regulations.

Should you have any questions or comments concerning this submission, please contact Mr. Edward Nellis at (973) 325-4904.

Sincerely,

A handwritten signature in black ink, appearing to read "Edwina Muir" followed by "(for)" in parentheses.

Edwina Muir
Director, Regulatory Affairs

EN/cjw

Encl.

Submitted via Federal Express Airbill No. 810494769547

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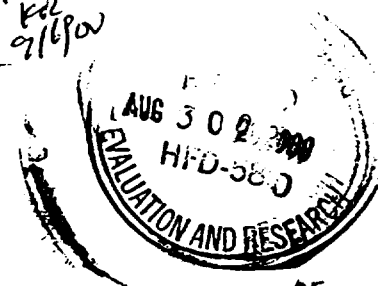
Organon Inc.

August 29, 2000

Electronic Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD 20852



Notice NAE for 9/6/00



NDA No. 21-187
NuvaRing® (etonogestrel/ethinyl estradiol ring)
NDA Amendment

initial 5/12 9/6/00

Dear Sir/Madam:

Reference is made to our original New Drug Application for NuvaRing® (etonogestrel/ethinyl estradiol ring), submitted on December 28, 1999. At this time, we are submitting additional NDA documentation in the form of an electronic and paper submission.

Electronic files enclosed herein are supplied on 1 CD-ROM (total file size is approximately 2 MB). The CD-ROM was checked for viruses using McAfee Vshield (ver: 4.0.3). The paper copy has been sent under separate cover to the Division Document Room, HFD-580.

Please note that Organon Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of 18 U.S.C. and Title 21 of the Code of Federal Regulations.

Should you have any questions or comments regarding this submission, please contact Mr. Edward Nellis, Assistant Manager of Regulatory Affairs at (973) 325-4904.

Sincerely,

Edwina L. Muir (for)

Edwina L. Muir
Director, Regulatory Affairs

Enclosure (1 CD-ROM)
Form FDA 356h

Submitted via Federal Express No. 8198 2930 7298

NAE 9/6/00
Muir



REVIEWS COMPLETED		
CSD ACTION		
<input type="checkbox"/> LETTER	<input checked="" type="checkbox"/> FINAL	<input type="checkbox"/> MEMO

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Organon Inc.

August 11, 2000

Dr. Karl Lin
Division of Biometrics II
Center for Drug Evaluation and Research (HFD-715)
Office of Biostatistics
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 21-187
NuvaRing® (etonogestrel / ethinyl estradiol ring)
**SAS TRANSPORT FILE (Tumor Dataset for
2-year Carcinogenicity Study)**

Dear Dr. Lin:

Reference is made to our New Drug Application (No. 21-187) for NuvaRing® (etonogestrel / ethinyl estradiol ring) which was submitted on December 28, 1999. Further reference is made to your telephone conversations on July 21, 2000 and August 8, 2000 with Mr. Edward Nellis (Organon Inc.) which involved your request for electronic datasets for the 2-year carcinogenicity study (SDGRR No.4412).

As agreed, Organon is hereby providing you with a SAS Transport File for the tumor dataset for the aforementioned carcinogenicity study. The enclosed electronic file ("tumor.xpt") is being supplied on one [1] CD-ROM disk (total file size approximately 146 kB). The CD-ROM was checked for viruses using McAfee Vshield (ver:4.0.3).

Please note that Organon Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of 18 U.S.C. and Title 21 of the Code of Federal Regulations.

Should you have any questions or comments concerning this submission, please contact Mr. Edward Nellis at (973) 325-4904.

Sincerely,

Edwina Muir
Director, Regulatory Affairs

EN/hpm

Enclosure

Submitted via Federal Express Airbill No. 8198 2930 6751

cc: Dr. Susan Allen / HFD-580 / 17B45 (w/o encl.)
Submitted via Federal Express Airbill No. 8198 2930 6762

Dr. Krishan Raheja / HFD-580 / 17B30 (w/o encl.)
Submitted via Federal Express Airbill No. 8197 5503 4688



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Organon Inc.

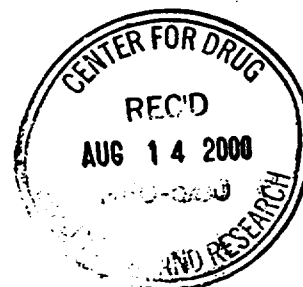
August 10, 2000

ORIGINAL

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Susan Allen, M.D., Director
Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation III
Document Control Room 17B45
5600 Fishers Lane
Rockville, Maryland 20857

ORIG AMENDMENT
BP



NDA No. 21-187
NuvaRing® (etonogestrel /
ethinyl estradiol ring)
Response to Reviewers' Requests

Dear Dr. Allen:

Reference is made to our New Drug Application (No. 21-187) for NuvaRing® (etonogestrel / ethinyl estradiol ring) which was submitted on December 28, 1999. Further reference is made to the July 21, 2000 FDA Letter wherein certain additional information (pertinent to the review of the NDA Pharmacology / Toxicology Section) was requested by FDA.

The Organon responses to the aforementioned FDA information requests are provided herein. The original FDA requests are repeated below (bold type) for the convenience of the reader:

1. **"Please inform the Division whether the 2-year carcinogenicity data has been submitted to the Division of Biometrics for review. If it has not been submitted, please contact Dr. Karl Lin at 301-827-3093 for instructions on the submission of the datasets."**

Organon Response

The "2-year Carcinogenicity Study" (Organon SDGRR No. 4412; [redacted] Study No. 92-2195) had been previously submitted to the CCVR (NuvaRing®) IND No. [redacted] on March 13, 1997 [redacted] and again on July 9, 1998 [redacted]. The 2nd (July 9th) IND submission had been intended for the Division of Biometrics representative (as requested by Dr. Raheja on February 6, 1998). However, since this submission was addressed to the DRUDP Director, it may not have been received by the DOBII representative for whom it was intended. A copy of this study report was also provided in the original NuvaRing NDA (volumes 45-52). It became apparent that the Division of Biometrics representative had not received the study report when Organon was contacted by Dr. Raheja on July 18, 2000 to again request that a copy of this report be sent to Biometrics (Dr. Karl Lin, DOBII). A full desk copy of this report has since been provided to Dr. Lin (on July 24, 2000). Dr. Lin confirmed receipt of the paper copy of the report via telephone on August 8, 2000.



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Dr. Lin had also requested that Organon provide SAS (electronic) datasets for this study to facilitate his review (Ref: July 21, 2000 telephone conversation with Dr. Lin). At that time the Organon representative (Mr. Edward Nellis) had indicated to Dr. Lin that the Agency had previously agreed to grant Organon a waiver for the electronic dataset requirement for the NuvaRing NDA (Ref: October 14, 1999 IND No. [REDACTED]). Dr. Lin suggested that if the full complement of datasets wasn't available electronically, perhaps it might be possible to provide a SAS Transport File for just the "Tumor Dataset". In the interest of facilitating the NDA review, Organon agreed to compile an electronic "Tumor Dataset" from the original paper hardcopy data. This electronic dataset (i.e. "SAS Transport File") will be provided directly to Dr. Lin under separate cover (with a copy of the submission cover letter being provided to the DRUDP Division Director).

2. **Please submit the pharmacokinetic data for 3-keto desogestrel from the rat carcinogenicity study conducted with desogestrel that was requested in the Agency's letter dated July 27, 1998.**

Organon Response

Within the framework of the rat carcinogenicity study conducted with desogestrel (HRCR ORG/128/80376), the 3-keto desogestrel levels were not determined since no plasma samples were taken. The pharmacokinetic data as requested by FDA is therefore unavailable.

3. **Please provide compilation of all neoplastic histopathological alterations for Table (Neoplasm Classification Summary) on page 0184, Volume 45 of the NDA. Please indicate its location in the NDA if it has already been submitted.**

Organon Response

The requested documentation may be found in Appendix-G / Table IIIC (on pages G-173 through G-257) of the original study report (SDGRR No. 4412); "Expanded Incidence Summary of Microscopic Postmortem Findings / All Animals". This information may be found in NDA Volume No. 46 (pages 0154 - 0238).

4. **Please provide organ weight data requested in the Agency's letter dated July 27, 1998.**

Organon Response

Within the framework of the rat carcinogenicity study conducted with desogestrel (HRCR ORG/128/80376), no organ weight data was collected. This information is therefore unavailable for submission.

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE

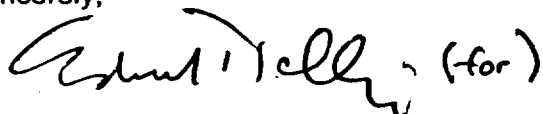
Susan Allen, M.D., Director
August 10, 2000
Page 3

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Please note that Organon Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of 18 U.S.C. and Title 21 of the Code of Federal Regulations.

Should you have any questions or comments concerning this submission, please contact Mr. Edward Nellis at (973) 325-4904.

Sincerely,

A handwritten signature in black ink, appearing to read "Edwina Muir (for)".

Edwina Muir
Director, Regulatory Affairs

EN/cjw

Enclosures
FDA Form 356h

Submitted in Duplicate
via Federal Express Airbill No. 810494769591

cc: Dr. Krishan Raheja / HFD-580 / 17B30 (Desk Copy)
Submitted via Federal Express Airbill No. 810494769606

Dr. Karl Lin / HFD-715 / 10B06 (Desk Copy)
Submitted via Federal Express Airbill No. 810494769617